General Remarks

The Applicants have reviewed the Examiner's comments and disagree. However, and in no way acquiescing to the Examiner's arguments, expressly reserving the right to prosecute the same or similar claims, certain claims have been amended and canceled in order to further prosecution. In order to further define an embodiment of the invention, a new dependent claim 18, in which the definitions of m, n, R^3 and p have limitations as follows:

- m is 0, 1 or 2; wherein the values of R^1 are the same or different (support can be found at page 12, line 27);
- n is 0 (support can be found at page 13, line 3);
- R^3 is amino (support can be found at page 13, line 6); and
- p is 0 (support can be found at page 13, line 14).

35 USC §112

Deleting the reference to "..in vivo hydrolysable ester or amide.." from claims 1, 8, 9, 10, 11 and 16 overcomes the indefiniteness rejection at point 1 of the Office Action. This amendment also overcomes the enablement rejection on pages 5 to 7 of the Office Action.

Claims are indefinite when, read in light of the specification, they do not reasonably apprise those skilled in the art of the scope of the invention. *Howmedia Osteonics v. Tranquil Prospects,* 401 F.3d 1367, 1371 (Fed. Cir. 2005). However, the claims must be so insolubly ambiguous that no narrowing construction can properly be adopted. When a claim "is not insolubly ambiguous, it is not invalid for indefiniteness." *Bancorp v. Hartford Life*, 359 F.3d 1367, 1372 (Fed. Cir. 2004). Claims need not be plain on their face in order to avoid condemnation for indefiniteness; rather, what the examiner is asked is whether the claims are amenable to construction. *SmithKline v. Apotex*, 403 F.3d 1331, 1340 (Fed. Cir. 2005), citing *Exxon Research & Engineering Corp. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

With regard to the rejection at point 2 on Page 4 of the Office Action, the Examiner argues that the presence of the word "including" in the definition of the variable groups in claims 1, 3, 8 and 9 on the basis that it renders these claims, and their dependent claims, indefinite. The

Examiner's rejection appears to be based on the assertion that this word somehow leaves the claim open for the inclusion of unspecified ingredients. Applicants do not agree with this point of view. On the contrary, Applicants believe the inclusion of this term actually improves the clarity of the claims.

For example, in the definition of R^1, the word "including" is used to clarify that an R^1 group including a group (B-E-), which represents one possible value of R^1, may possess a further optional substituent. Therefore, the word including is merely present to make it clear that all possible values of R^1 may possess an optional substituent and, for the avoidance of any doubt, this includes the groups (B-E-). This word is used in a similar manner in the definition of the W and Q groups. The use of this word does not introduce any ambiguity or allow the inclusion of unspecified ingredients and therefore does not render the claims indefinite.

The Examiner has rejected claims 14 and 16 on the ground of lack of enablement. The rejection to claim 14 has been addressed by deleting this claim. However, Applicants do not agree with the Examiner's rejection to claim 16, which is directed to a method of treating cancer. It is also not clear to us why the Examiner has acknowledged that the specification is enabling for breast cancer but not enabling for all other cancers.

Applicants note that the Examiner has referred to a particular article (*Ragione et al*) in coming to his decision regarding enablement. This article shows that HDAC inhibitory effects are unpredictable and exploratory. However, Applicants do not feel it is appropriate to use conclusions from this article to provide a broad indication of the state of the art in relation to the potential use of HDAC inhibitors for the treatment of cancer. The research work disclosed in the article is directed only at the identification of genes that are modulated by butyrate. Indeed, the conclusion of the article states that the work contributes to the elucidation of the molecular effects of butyrate. The work therefore does not provide an overall view of the potential effects and uses of HDAC inhibitors.

Applicants believe the articles referred to in the introduction of the present application are more appropriate for providing such a general indication of the state of the art. The application, at lines 4 to 6 of page 1, states that compounds having HDAC inhibitory activity have value in the treatment of disease states associated with cancer (Marks et al., *Nature Reviews, 1, 194-202, (2001)*). This particular article, entitled Histone deacetylases and Cancer: causes and therapies, indicates that at the time of it's publication, several HDAC inhibitors were in clinical trials and

that anti-cancer activity for these inhibitors had been observed in various cancers. Indeed the concluding paragraph reads:

"Clinical trials show that HDAC inhibitors are well tolerated, can inhibit HDAC activity in peripheral mononuclear cells and tumours and, more importantly, have clinical activity with objective tumour regression."

The current specification also states that "inhibitors, such as Trichostatin A (a natural product isolated from *Streptomyces hygroscopicus*), have been shown to exhibit significant anti-tumour effects and inhibition of cell-growth (Meinke, P. T., *Current Medicinal Chemistry*, 8, 211-235 (2001))" [see page 1 lines 29-32] and that Trichostatin A has amongst other things been shown to prevent the formation of tumours in mice (Finnin et al., *Nature, 401, 188-193 (1999)*).

The above references provide strong evidence that an established link between HDAC inhibitory activity and potential use in various cancers was present at the time of filing the original application. The specification also provides extensive evidence to demonstrate that compounds of the present invention exhibit HDAC inhibitory activity. In total, three biological assays have been used to confirm the HDAC-inhibitory properties of the claimed compounds (see line 19 of page 20 through to line 13 of page 22). These comprise both enzyme and cell assays, confirming that compounds of the invention not only have inhibitory activity against the enzyme, but are also capable of gaining access to and inhibiting the enzyme target within whole cells.

In view of the extensive assay disclosure, together with the state of the art at the time of filing, Applicants consider it reasonable that the claim refers to the treatment of cancer in general, rather then being restricted to one specific cancer.

35 USC § 103

Applicants note that the Examiner has asserted that WO 01/38322 is relevant to the inventive step of the claims currently on file. However, after reviewing the Examiner's specific comments, it appears to us that his arguments actually relate to WO 03/024448 (also cited in the

ISR) rather than WO 01/38322. Applicants seek further clarification on this point; however, in order to further prosecution the Applicants submit the following.

If the Examiner did indeed intend to refer to WO 01/38322, then Applicants disagree for the following reasons:

WO 01/38322 discloses a broad group of histone deacetylase inhibitory compounds, all of which must comprise a linker group L^1 between the Cy and Ar groups (which correspond to Ring A and the phenyl ring of the benzamide group in our compounds of formula I respectively). Significantly, the linker group L^1 **cannot** be a direct bond (L^1 must be a group $-(CH_2)_m$-W-, where m is 0-4 and W is selected from –C(O)NH-, -$S(O)_2$NH-, -NHC(O)-, -$S(O)_2$NH- and –NH-CO-NH-). This means that the Cy group in WO 01/38322 **cannot** be directly linked to the Ar group. This clearly contrasts with our claim 1, where ring A (which corresponds with Cy) **must be** directly linked to the 4 position of phenyl ring of the benzamide group (which corresponds with Ar).

Therefore, WO 01/38322 clearly teaches away from the compounds defined in our claim 1 by specifying that a linker group L^1 is an essential element of the compounds it describes. Consequently, WO 01/38322 provides no motivation whatsoever for a skilled person to consider departing from this teaching and contemplate preparing compounds in which a piperidinyl group (specifically) is directly linked to the 4-position of a benzamide group. For this reason, Applicants consider the claims defined in the new claim 1 to be inventive over the disclosure in WO 01/38322.

If, on the other hand, the Examiner intended to refer to WO 03/024448, then Applicants have the following comments:

WO 03/024448 discloses a broad group of benzamide compounds that are indicated to be inhibitors of the enzyme histone deacetylase. Applicants acknowledge that the Examiner considers claim 1 to be novel over the disclosure in WO 03/024448.

With regard to the obviousness of the claimed compounds, the Examiner asserts that although a piperdinyl ring has not been exemplified as a value for Cy^3 (which corresponds to

Ring A in the present application), WO 03/024448 teaches equivalency by virtue of the compounds taught in Table 5f. Applicants strongly disagree with this point of view and believe there is no specific teaching in WO 03/024448 that points towards the compounds defined in claim 1.

WO 03/024448 discloses 7 quite different generic structural formulae. However, only three of these formulae (namely Formula 2, 3 and 3(b)) allow the possibility of having a heterocyclyl ring directly attached to a phenyl ring of a benzamide group, as is the case for our compounds of Formula I. Furthermore, in order for the skilled person to focus on such compounds, he would need to select this particular combination and configuration of groups from a wide range of possible options provided in WO 03/024448. For example, in Formula 3, Ar^3 can be arylene (which itself can be any C_6-C_{14} aromatic moiety comprising one to three aromatic rings) or heteroarylene, Cy^3 can be cycloalkyl, aryl, heteroaryl or heterocyclyl and the linker group X^2 can be a chemical bond, L^3, W^1-L^3, L^3-W^1, W^1-L^3-W^1, or an L^3-W^1-L^3 group. Thus in order to move towards the presently claimed compounds, the skilled person would have to make a number of specific selections. Applicants believe there is no teaching in the specification to motivate the skilled person to do this. In fact to the contrary, the general teaching in the specification would motivate the skilled person to move away from the claimed compounds. For example, paragraph 84 on Page 26 states that X^2 group in Formula 3 is preferably selected form L^3, W^1-L^3, L^3-W^1, W^1-L^3-W^1, and L^3-W^1-L^3. This preference for having a linker group is also apparent in the experimental examples. There are only 15 exemplified compounds (from a total of 592) in which a heterocycly group is directly attached to a phenyl ring of a benzamide group. Even if the skilled person would for some reason be interested in the compounds with a heterocyclyl ring directly linked to the 4-position of a benzamide group, none of the 15 exemplified compounds mentioned above actually have piperidinyl as the heterocycly ring. In fact, none of the Examples in Table 5f (which the Examiner asserts teach equivalency to the claimed invention) have a piperidinyl ring **directly or even indirectly** linked to the 4-position of a benzamide group either. Therefore, there is nothing in WO 03/024448 that teaches or suggests the particular compounds defined in claim 1 of the present application.

Applicants therefore believe that the claimed compounds are both novel and inventive.

Double patenting

As this rejection is provisional, Applicants do not propose to take any further action at this stage.

Conclusion

The Applicants believe that the claims are allowable and a timely Notice of Allowance is requested. A petition for a one-month extension of time is being filed herewith. The Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 100690-1P US.

Although Applicants believe no further fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 100690-1P US.

Respectfully submitted,

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